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10/598,073	08/17/2006	Ester Fernandez-Salas	17596(BOT)	9808

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	PAPER NUMBER
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03/17/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/598,073	FERNANDEZ-SALAS ET AL.	
	Examiner	Art Unit	
	GINNY PORTNER	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *2,3,9-15 and 23-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-8,16-22,28-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-33 are pending; claims 34-78 have been canceled. Claims 1, 4-8, 16-22, 28-33 are under consideration. Claims 2-3, 9-15, and 23-27 are withdrawn from consideration.

Rejections withdrawn

2. Claims 1 and 4 rejected under 35 U.S.C. 102(e) as being anticipated by Nebrigic (US PG-Pub 2005/0040907 , filing date March 17, 2003, international 371 filing date September 20, 2001, published in English, designated the US) is herein withdrawn in light of the amendment of independent claim 1 to recite the presence of SNAP-25 to be present in the cell, and the cells of Nebrigic are not described to comprise a SNAP-25 receptor, nor are the type cell specifically described other than comprising FGFR3 receptors.

3. Claims 1, 18, 28-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Steward et al (1 common inventor, Aoki, and common Assignee, Allergan, US Pat.7,208,285) is herein withdrawn inlight of the amendment of claim 1 to recite the phrase "endogenous SNAP-25".

4. Claims 1, 4-8, 16-22, 28-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-9, 28-32, 39 of U.S. Patent No7,183,066 (also known as US PG-pub2004/0072270) is herein withdrawn inlight of the amendment of claim 1 to recite the phrase "endogenous SNAP-25".

5. Claims 1, 18, 28-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-8, 27, 29, 31-35,50, 58,66-67,69-771,84 of U.S. Patent No. 7,208,285 (also known as US PG-pub2003/0143650) is herein withdrawn in light of the amendment of claim 1 to recite the phrase "endogenous SNAP-25".

Response to Amendment

6. The Declaration of Dr. Ester Fernandez-Salas under 37 CFR 1.132 filed December 12, 2008 is insufficient to overcome the rejection of claims 1, 4-8, 16-22, 28-33 based upon Keller et al, or Steward et al and Fernandez-Salas et al as set forth in the last Office action because:

7. While Dr. Fernandez-Salas clearly discusses the relationship between transformation of a cell with a gene for producing a genetically engineered cell, which results in a protein that is

recombinantly produced, the Declaration is not commensurate in scope with what is not claimed, which includes (see claim 19 which depends from claims 18 and independent claim 1), "a primary neuronal cell".

8. The primary neuronal cells of claim 19 are not claimed to be a transformed primary neuronal cell culture that have been genetically engineered to express a recombinant protein. Primary neuronal cells originate from a natural source and express wild type receptors; Applicant's Specification states that wild-type FGFR3 receptors are within the scope of their claims. Primary neuronal cells have wild type FGFR3 receptors on the outside of the cell surface, exogenously expressed, and endogenously comprises SNAP-25. Applicant's definitions of their invention includes both wild type and recombinant cells, but no specific recombinant cells are now claimed. No specific DNA coding sequences have been introduced into the cells and Applicant claims the use of a"primary neuronal cell" (claim 19).

9. None of the claims recite phrases such as ---recombinantly expressed---, ---genetically engineered----, ----heterologous-----, ----- transformed with a heterologous coding sequence for FGFR3---- nor ------transfected----. None of the cells of the claims have been transfected with a heterologous coding sequence for FGFR3.

10. The Declaration is not commensurate in scope with the instantly claimed invention, based upon the claim limitations recited, and the various embodiments disclosed that include wild type receptors on a primary cultured cell.

Response to Arguments

11. Applicant's arguments filed December 15, 2008 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 102

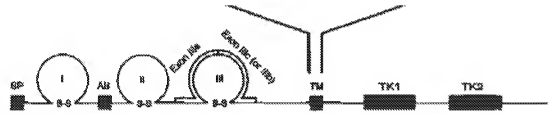
1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Please Note: The following prior art rejections are being made of record in light of the fact that Applicant's definition for FGFR3 receptor includes that wild-type, naturally occurring FGFR3 receptor that is associated with the surface of neuronal cells: Instant Application paragraphs [0034]…… "FGFR3 as a cell surface receptor" and [0035] As used herein, the term "Fibroblast Growth Factor 3 Receptor" is synonymous with "FGFR3" and means a FGFR3 peptide or peptidomimetic which binds BoNT/A in a manner that elicits a BoNT/A intoxication response. FGFR3s useful in the invention encompass, without limitation, **wild type FGFR3s**,

Additionally, the term "exogenous" is being read to include Applicant's wild type species of FGFR3 that is outside the cell membrane, a cell surface receptor that exists at a location that is exogenous to the cell cytoplasm. "TM" is transmembrane, TK1 and TK2 are cytoplasmic kinase domains, I, II and III are exogenous, cell surface domains of FGFR3 known to be present in mammalian neuronal cells.



FGFR3

2. The rejection of claims 1, 4, 7, 16-17, 18-19, 22, 28-29 under 35 U.S.C. 102(b) as being anticipated by Keller et al (1999, reference of record) is traversed on the grounds that:

a. "Present specification at ¶ 34. In addition, the cell can be a neuronal or non-neuronal cell "that express low or undetectable levels of endogenous receptor, but which have been transfected with, or otherwise engineered to express, one or more exogenous nucleic acid molecules encoding one or more FGFR3s"; and "e.g., genetically engineered variants".

b. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., express low or undetectable levels of endogenous receptor, but which have been transfected with, or otherwise engineered to express, one or more exogenous nucleic acid molecules encoding one or more FGFR3s; genetically engineered variants") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

c. Applicant's claims include wild type spinal cord cells (see definition provided at paragraphs [036]] are wild type naturally occurring FGFR3 containing cells.

FGFR3s useful in the invention encompass, without limitation, wild type FGFR3s, naturally occurring FGFR3 variants, non-naturally FGFR3 variants, The

examiner's rational is based upon Applicant's described embodiments (quoted portion set forth immediately above).

Spinal and neuronal cells comprise wild type, naturally occurring FGFR3 receptors that have both exogenous (outside the cell) as well endogenous (inside the cell) domains. The claimed cells have not been structurally distinguished from the cells of the applied prior art.

The method of Claim 19 ("said neuronal cell is a primary neuronal cell") is directed to the use of primary cell cultured cells. The primary neuronal cells are not transfected, nor transformed, and are clearly within the scope of Applicant's claimed invention of claims 1 and 4. Claim 19 provides evidence of the fact that the claims encompass naturally occurring FGFR3 receptors, present in a primary culture of neuronal cells, the FGFR3 receptor domain being exogenously expressed on the outside surface of the cell. None of the claims recite the phrase genetically engineered.

While claim 20 recites the phrase "immortalized neuronal cell", the immortalized neuronal cell has not been transfected by genetic engineering to produce a heterologous FGFR3 receptor. Claim 21 recites the phrase "transformed neuronal cell", but what the cell is transformed with, is not specifically claimed and therefore may be transformed with type of genetic information/mutation.

The examiner's position is based upon an evidentiary basis, specifically Applicant's claims, and described embodiments, and the knowledge of the FGFR3's

multidomain structure. The prior art rejection is maintained for reasons of record and responses set forth herein.

3. Keller et al (1999) disclose the instantly claimed invention directed to a method, the method comprising the steps of:

d. **Contacting a sample** (botulinum toxin A obtained from Wako Chemicals, Richmond, VA, the toxin being a preparation/formulation of a purified commercial product, see page 138, section 2.5) to **a cell** that contains an exogenous FGFR3 (cell is a spinal cord (type of neuronal cell) cell culture (mice) that comprises a neuronal component (see page 138, sections 2.3, 2.4, 2.5, 3.1 and Figure 1) the spinal cord cell culture presenting a wild type naturally occurring receptor for botulinum toxin type A which is encompassed by Applicant's definition at Specification [0035])] the exogenous, cell surface receptor binding to BoNT/A complex (see section 2.5, page 138) which resulted in transport of BoNT/A and

e. **Detecting** botulinum toxin type A activity relative to a control cell (Intact SNAP-25, Figure 1, lane 1), wherein the difference in activity (cleavage of SNAP-25, lane 2, Figure 1) is indicative of botulinum toxin type A activity (see Figure 1).

While Keller et al does not specifically describe the lectin and protein receptors present in the spinal cell culture for BoNT/A, the spinal cell culture inherently comprised the polysialoganglioside, and a FGFR3 receptor because the botulinum toxin successfully was translocated across the membrane of the primary cultured spinal cells and cleaved by proteolysis SNAP-25, botulinum toxin type A's substrate (see Figure 1, ledger narrative).

Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

Inherently the reference anticipates the now claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. The Court further held that this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art .

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 5-6,8, 20-21 and 30-33 rejected under 35 U.S.C. 103(a) as being unpatentable Keller et al as applied to claims 1, 4, 7, 16-19, 22 and 28-29 over Fernandez-Salas et al (US Patent 7,183,066).

See discussion of Keller et al above. Keller et al describe and teach a method of detecting BoNT/A activity in a biological sample, the method comprising contacting a neuronal cell from mice with a sample and detecting cleavage of SNAP-25 relative to a control sample but differs from the instantly claimed invention by failing to show alternative types of neuronal cells and biological samples that can be used in the assay method.

Fernandez-Salas et al describe a method encompassing the use of mouse cells, as well as alternative type cells (rat, human, bovine), as well as additional sources of biological sample in which BoNT/A activity can be measured in an analogous art for the purpose of describing a cell based assay for detecting BoNT/A activity.

Fernandez-Salas et al The term "cell," as used herein, means any eukaryotic cell that expresses,.....at least one receptor that binds a clostridial toxin. The term cell encompasses, without limitation, primary cells; cultured cells; established cells; normal cells; transformed cells; tumor cells;....cells of a variety of species and cell types. Thus, the term cell encompasses, without limitation, mammalian cells such as murine, rat, ... bovine, ...and human cells. A variety of cells are useful in the invention including, without limitation, primary cells; established cells; human cells; neuronal cells such as primary neurons, established neurons and human neurons

A variety of cells are useful in the invention including, without limitation, primary cells; established cells; human cells; neuronal cells such as primary neurons, established neurons and human neurons; and non-neuronal cells, which can be, for example, glandular cells such as pancreatic acinar cells. Neurons useful in the invention include CNS neurons and peripheral neurons; as non-limiting examples, such neurons include neuroblastoma cells, spinal cord neurons, dorsal root ganglion neurons, cerebral cortex neurons, cerebellar neurons, hippocampal neurons and motor neurons.

A neuron useful in the invention can be a peripheral neuron or CNS neuron; as non-limiting examples, spinal cord neurons such as an embryonic spinal cord neurons, dorsal root ganglia (DRG) neurons, cerebral cortex neurons, cerebellar neurons, hippocampal neurons and motor neurons can be useful in the invention as described further below.

Exemplary neurons useful in the invention include, but are not limited to, primary cultures of embryonic DRG neurons, for example, primary cultures of embryonic rat DRG neurons as described in Welch et al., Toxicon 38:245 258 (2000); and primary cultures of fetal spinal cord neurons, for example, primary cultures of murine fetal spinal cord neurons as described in Neale et al., J. Cell Biol. 147:1249 1260 (1999), or Chaddock et al., Infect. Immun. 68:2587 2593 (2000)).

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Exemplary neuronal cell lines useful in the invention include, without limitation, neuroblastoma cell lines such as LA-N-2, SH-SY5Y, N2a, NS-20Y and NIE-115; hybrid cell lines, including neuroblastoma/glioma hybrids such as NG108-C15; motor neuron cell lines such as NSC-34 and NSC-19; spinal cord cell lines such as M4b; CNS cell lines; cerebral cortex cell lines such as CNh; dorsal root ganglion cell lines such as G4b; hippocampal cell lines such as HT-22; and pheochromocytoma cell lines such as PC12.

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A neuronal cell line useful in the invention can be, for example, a neuroblastoma cell line such as a murine, primate or human neuroblastoma cell line. Exemplary neuroblastoma cell lines useful in the invention include, without limitation, LA-N-2, SH-SY5Y, N2a, NS-20Y and NIE-115. As an example, the invention can be practiced with the LA-N-2 human neuroblastoma cell line, which has properties of cholinergic neurons and expresses well characterized cholinergic markers (Rylett et al., J. Neurochem. 61:1388 1397 (1993); Singh et al., J. Neurosci. Res. 25:476 485 (1990); and Yeh et al., Neuroscience 27:309 315 (1988)). As a further example, the invention can be practiced with the SH-SY5Y human neuroblastoma cell line, which exhibits inhibition of [.sup.3H]-noradrenaline release induced by K.sup.+/Ca.sup.2+ upon exposure to botulinum toxin (Purkiss et al., Neurotoxicology 22:447 453 (2001)).

Fernandez-Salas et al "sample" means any biological matter that contains or potentially contains an active clostridial toxin. Thus, the term sample encompasses but is not limited to purified or partially purified clostridial toxin; recombinant single chain or dichain toxin with a naturally or non-naturally occurring sequence; recombinant clostridial toxin with a modified protease specificity; recombinant clostridial toxin with an altered cell specificity; chimeric toxin containing structural elements from multiple clostridial toxin species or subtypes; bulk toxin; formulated product; cells or crude, fractionated or partially purified cell lysates, for example, engineered to include a recombinant nucleic acid encoding a clostridial toxin; bacterial, baculoviral and yeast lysates; raw, cooked, partially cooked or processed foods; beverages; animal feed; soil samples; water samples; pond sediments; lotions; cosmetics; and clinical formulations. It further is understood that the term sample encompasses tissue samples, including, without limitation, mammalian tissue samples, livestock tissue samples such as sheep, cow and pig tissue samples; primate tissue samples; and human tissue samples. Such samples encompass, without limitation, intestinal samples such as infant intestinal samples, and tissue samples obtained from a wound."

It would have been obvious to the person of ordinary skill in the art to modify the method of Keller with the alternative cells and samples as taught by Fernandez-Salas et al because both Keller and Fernandez-Salas et al teach neuronal cell based detection methods for BoNT/A activity in a sample and Fernandez-Salas et al teach and show additional sources of neuronal cells and samples that are known in the art that will provide ready means for measuring BoNT/A activity.

In the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of detecting BoNT/A activity in a sample with a cell based assay because both Keller and Fernandez-Salas et al were successful in measuring/detecting BoNT/A in the samples relative to a control cell based upon SNAP-25 cleavage detection.

It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose: idea of combining flows logically from their having been individually taught in the prior art" In re Kerkhoven (205 USPQ 1069, CCPA 1980

Additionally, *KSR International Co. v. Teleflex Inc*., 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method , and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc*., 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art (Keller et al) to use a neuronal cell based assay for detection of botulinum toxin activity in a biological sample and Fernandez-Salas et al teach alternative sources and samples of neuronal cells, such as immortalized cells, so repeated preparation of primary neuronal cells need not be prepared before each assay. Thus, it would be obvious to apply a known technique to detect a known biological activity (BoNT/A) in samples to be used in a known method that is ready for improvement with alternative sources of neural cells to yield predictable results.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GINNY PORTNER whose telephone number is (571)272-0862. The examiner can normally be reached on flextime, but usually M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ginny Portner/
Examiner, Art Unit 1645
March 14, 2008

/Robert B Mondesi/
Supervisory Patent Examiner, Art Unit 1645